HONEY, COPPER, WINE AND WOUND INFECTION

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Wound healing and its possible impairment has been a concern since the origin of mankind. No wonder that the most ancient written documents tell us how to take care of wounds.

SUMER

The surviving Mesopotamian medical records consist of roughly 1,000 cuneiform tablets. From the scientists who were able to decipher some of these 4,000 year old Sumerian tablets (Fig.1), we learn that three gestures should be made to treat a wound: washing, making a plaster and bandaging. The Sumerians were great beer lovers; it was thus natural that they would use it in their recipe: "wash the diseased part with beer of good quality and hot water, and rub with the mixture." According to their clay tablets, the plasters they used were made of mud: "take some river sediment, pound it, knead it with water then rub the diseased with mineral oil and bind it as a plaster."

Figure 1- Sumerian cuneiform writing tablet

EGYPT

Egyptian medicine as recorded in the Smith papyrus (1650 BC) went further in dealing with wounds. The basic wound salve was a mixture of grease, honey and lint. The lint was some sort of vegetable fiber, the grease could be anything from vegetable oil to snake grease. The honey was by far the most popular Egyptian drug, being mentioned some 500 times in 900 remedies. It came from wild bees since Egyptians did not practice apiculture.

HONEY

Honey is antibacterial for several reasons.

- Being extremely hypertonic, it draws water from the bacterial cells, causing them to shrivel and die.
- Honey can also prevent the growth of bacteria by an antibiotic mechanism. One of the active principles, *inhibine* or glucose-oxydase, is an enzyme secreted by the pharyngeal glands of the bee.
- High concentration of *Staphylococci* or *E. coli* added to a mixture made of butter and honey cannot survive more than 2 to 3 days.
- Honey is still in use in several parts of the globe for the treatment of burns.

GREECE

Peri Helkon (Περί έλκων) is the title of a whole Hippocratic treatise about wounds and the way to treat them. The word *helkon* in ancient Greek can be translated as wound or ulcer, which today is usually a complication of an infected wound. The Greeks had noted that after a few days, a white-yellowish secretion covered most deep wounds with more or less odor. They had ambivalent feeling about this pus. The turbid and smelly variety was called *ichor* (ιχώρ). It was a kind of corrupted blood, which could lead to *sipsi* (σήψις) – sepsis – putrefaction or gangrene. It was thus to be treated by removing the bad blood flooding to the wound. Letting blood escape from the body even at a distance from the wound was one of the treatments and is at the origin of the traditional surgical veno-sections that lasted up to the 19th century. The non-smelly good white pus, the *phlegma* (φλέγμα), was considered a good omen and became also for centuries the pus *bonum et laudabile* of the Romans, that generations of surgeons did everything to enhance in order to promote healing. Despite these theories, the Greeks could not fail to notice that many wounds healed perfectly without suppuration. Therefore, every wound posed a dilemma: was it one that could heal directly or one that should be helped to suppurate?

In case they had decided to prevent suppuration, they used dry powders to be sprinkled on the wound like lead, bronze, zinc or copper oxide. As was proved later on, these substances have strong anti-bacteriological powers. A mythological tale tells us how Telephos, the king of Mysia, was saved by this method. Telephos was wounded in the thigh by Achilles on his way to Troy. The wound would not heal and Telephos consulted the oracle of Delphi about it. The oracle responded in a mysterious way that "he that wounded shall heal." Telephos convinced Achilles to help heal his wound in return for showing the Achaeans the way to Troy. Achilles accepted and scraped some rust from his spear on the wound as depicted in a famous bas-relief found in Herculaneum (Fig.2). Did the oracle suspect the antibacterial power of copper?

Figure 2 - Telephos' wound healed by copper scraped from Achilles' spear

COPPER

Copper kills bacteria in two sequential steps.

- The first is a direct interaction between the surface and the bacterial outer membrane, causing the membrane to rupture.
- The second is related to the holes in the outer membrane, through which the cell loses vital nutrients and water, causing a general weakening. When the cell's main defense (its outer envelope) has been breached, there is an unopposed stream of copper ions entering the cell. The bacterium can no longer "breathe", "eat", "digest" or "create energy."

When the good pus had to be enhanced for better healing according to the theory, ancient Greeks were using other mixtures made of greasy wool, water and wine. Wool would certainly increase suppuration, but at the same time the alcoholic content of wine and its antiseptic properties had a beneficial effect on the infection. In fact, by cleansing wounds with wine, they were actually disinfecting them with polyphenol, a more complex version of the 19th century phenol that would be used by Lister.

WINE

10% concentrations of ethyl alcohol in ordinary wines have little effect on bacteria. The optimal strength of alcohol-water mixtures against *E. coli* and *Staphylococci* is 70%.

The effect of wine is also truly bactericidal, not bacteriostatic. Red wine is a little more effective than white, but the best antiseptic are the strong southern wines like port, among which the prize goes to Greek wine from Samos. This mechanism is not due to the alcoholic content of the wine, but to the *anthocyanes*, a subgroup in the large group of polyphenol present particularly in the principal pigment of red wine, malvoside or oenoside. Its antiseptic effect increases as the wine ages.

ROME

The Romans did not modify the treatment of wound infection, but we owe to the encyclopedist Cornelius Celsus (30 AD) the cardinal signs of inflammation that every medical student has learned: rubor, calor, dolor and tumor (redness, heat, pain and swelling). The Greek Galen (129AD-200AD), who greatly influenced the practice of medicine and surgery for generations, was a strong supporter of promoting "good pus" for better healing and nobody would dare to contradict him except Theodoric de Borgognoni who wrote in 1266: "It is not necessary that pus be present in the wounds as most surgeons believe. It is a great mistake; such a procedure is against nature, it prolongs the disease and delays the healing of the wound." Borgognoni was in favor of pouring wine on the wounds to stop suppuration, but his advice was quickly forgotten.

For generations of surgeons, up to the end of the 19th century, wound infection has been a major threat, particularly after limb amputations. The cause and prevention of these often- deadly complications arose following a series of observations and discoveries in the field of microbiology, chemistry and epidemiology.

MICROBIOLOGY: *THE ANIMALICULES IN THE MOUTH*

In 1665, Robert Hooke, an English naturalist, published an illustrated book entitled *Micrographia, or Some Physiological Descriptions of Minute Bodies Made by Magnifying Glasses* (Fig.3), with spectacular copperplate engravings of the miniature world, particularly of insects.

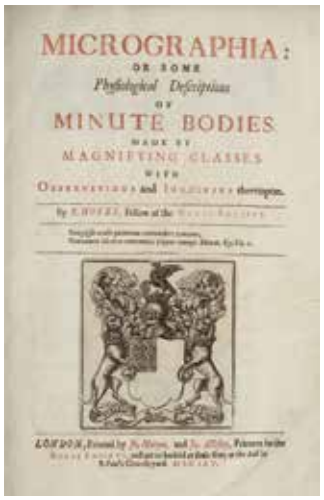


Figure 3 - Micrographia by Robin Hook

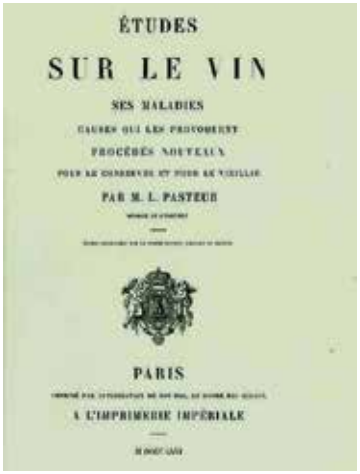
He also described cork and other plant tissues, introducing the term *cell* because the cellulose walls of dead cork reminded him of the blocks occupied by monks.

A few years later, the Dutchman, Anton Van Leeuwenhoek, fascinated by Hooke's observations, started developing his own magnifying lenses and microscopes. In 1683, he wrote to the Royal Society about his observations on the dental plaque found in people who had never cleaned their teeth in their lives and reported: "I then most always saw, with great wonder, that in the said matter there were many very little living animalicules, very prettily moving." He concluded: "All the people living in our United Netherlands are not as many as the living animals that we carry in our mouth." These were the first observations on living bacteria ever recorded, but most people were horrified by these findings and would not believe that they have so many animalicules in their mouth.

CHEMISTRY: THE WINE LOVERS

The word *antiseptic* was used for the first time by Sir John Pringle in a series of articles entitled *Experiments upon septic and antiseptic substances*, but these papers would have remained unknown had a French woman, Marie-Geneviève-Charlotte d'Arconville (Fig.4), not translated and corrected his experiments, doing for several years daily experimentation on the use of mercury and other substances as antiseptics to fight putrefaction. She published under a pseudonym in 1766 a book entitled *Essai pour servir à l'histoire de la putréfaction*, but wanted to remain anonymous because she thought that if people knew that a discovery had been made by a woman, it would not be taken seriously. Noticing a hundred years before Pasteur the link between putrefaction and fermentation and its importance for medicine, she wrote: "This marvelous operation that nature operates on the organized bodies (the acid fermentation leading to putrefaction) should excite our attention and made us work assiduously to discover its mechanism. Surgery and medicine could draw great advantages by this knowledge for the healing of numerous wounds and diseases."


Figure 4 - Portrait of Madame d'Arconville


ÉTUDES
SUR LE VIN
SES MALADIES
PAR M. L. PASTEUR
PARIS
Figure 5 - Book by Louis Pasteur on wine-making

If Italy and France had not been great wine lovers, germs and wound infections would have remained mysterious for a long time. It all started in Florence when Adamo Fabbroni wrote in 1787 a book on the art of making wine (*Ragionamento sull'arte di far vino*), where he affirms that wine fermentation is produced by living substances present in the must. This idea was sustained by several scientists, particularly by the chemist Louis Pasteur who owned a vineyard and had written a treaty on wine making (Fig.5).

His experiment was as follows. He would empty the pulp of grapes in a clean glass with no connection to the open air. The juice thus obtained did not show any fermentation. But adding of the skin of the grapes, contaminated by rainwater, provoked fermentation. He concluded that living substances, germs, yeasts, are normally present in our atmosphere. For this and for his other discoveries in the field of infectious diseases, Pasteur is often considered one of the greatest benefactors of humanity.

The notion that the air could contaminate tissues and fluids gave the idea to the British surgeon Joseph Lister to prevent wound infection with antiseptic drugs. He was aware that some peasants were using a phrenic acid based product in the fields to remove the smelly sewer odor without affecting the farm animals. His 1867 article on "Antiseptic principle in the practice of surgery" became a landmark in the history of surgery: "To prevent the occurrence of suppuration, with all its attendant risks, was an object manifestly desirable, but till lately apparently unattainable, since it seemed hopeless to attempt

to exclude oxygen, which was universally regarded as the agent by which putrefaction was effected. But when it had been shown by the researches of Pasteur that the septic property of the atmosphere depended, not on the oxygen or any gaseous constituent, but on minute organisms suspended in it, which owed their energy to their vitality, it occurred to me that decomposition in the injured part might be avoided without excluding the air, by applying as a dressing some material capable of destroying the life of the floating particles. The material, which I have employed, is carbolic or phenic acid, a volatile organic compound, which appears to exercise a peculiarly destructive influence upon low forms of life, and hence is the most powerful antiseptic with which we are at present acquainted." Thanks to this method, the incidence of wound infection of Lister's patients dropped considerably.

EPIDEMIOLOGY: THE DIRTY HANDS

The Hungarian gynecologist, Ignaz Philipp Semmelweis noticed that in two obstetrical clinics in Vienna there was a different incidence of puerperal fever. In one, attended only by midwifes, the incidence was low whereas in the other, where medical students came frequently from the autopsy room, the incidence of death by fever was high. In 1847, his friend Kolletschka, professor of anatomy died of an infection after having cut his finger during an autopsy. It was a trigger for his decision to ask the students to wash their hands with bleach before entering the obstetric ward. In two years, mortality fell from 15% to 1.5%. At that time, surgeons were very reluctant to adopt these procedures of hygiene. They were used to operate their patients dressed in city clothes or dirty blouses. Some of them even enjoyed having blood or pus on their outfit. It took almost twenty years for Semmelweis' principles to be applied in surgery and for Pasteur to declare: "If I had the honor to be a surgeon, knowing, as I am, all the dangers that the microbial germs can affect the surface of all the objects, especially in the hospitals, I would not only use perfectly cleaned instruments, but after having cleaned my hands with great care, I would use only bandages and sponges which were exposed before to a temperature of 130 to 150 degrees."

THE GENEVA HAND HYGIENE MODEL: *BACK TO ALCOHOL*

As Chief of prevention of infections at the Geneva University Hospital, the Swiss Didier Pittet observed that strict application of hand washing between each patient's care may prevent cross-infection by 50%, but health-care workers' adherence to guidelines was usually poor. For doctors and nurses, to wash hands with soap for five minutes between patients is time consuming and often avoided. Easy, timely access to both hand hygiene and skin protection is necessary for satisfactory hand hygiene behavior. Alcohol-based hand rubs have been found to be better than traditional hand washing as they require less time, act faster, are less irritating, and contribute to sustained improvement in compliance associated with decreased infection rates. In 2004, Pittet was approached by the World Health Organization's World Alliance of Patient Safety to lead the First Global Patient Safety Challenge under the banner "Clean Care is Safer Care". The mandate was to galvanize global commitment to tackle health-care associated infection, which had been identified as a significant area of risk for patients in all United Nations Member States. As of September 2017, "Clean Care is Safer Care" has been endorsed by ministers of health in over 150 countries worldwide – representing coverage of more than 90% of the world population. Alcohol-based hand rub is now also routinely practiced by most surgeons before entering the operating room.

Didier Pittet himself is not an alcohol drinker, but he was accused of promoting the use of alcohol in a few Muslim countries. Physiologists had to prove that the molecules of alcohol could not cross the skin barrier of the palms and enter the blood stream before the method was accepted.

in vino veritas